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05 JUL 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

TIMREL LIMITED
9, Myrtle Street
Douglas
Isle of Man IM1 1ED

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

British Virgin Islands

8419822001

4. Title of the invention

CONTROLLED RELEASE COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

5. Name of your agent *(if you have one)*

W. H. Beck, Greener & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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7 Stone Buildings
Lincoln's Inn
London WC2A 3SZ

Patents ADP number *(if you know it)*

323001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature W H Beck Greener & Co Date 05.07.02

12. Name and daytime telephone number of person to contact in the United Kingdom: Mr. Anthony F. Burford - (020) 7405 0921

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Controlled Release Composition for the Treatment of Inflammatory Bowel Disease

The present invention relates to the use of prednisolone metasulphobenzoate (11,17-dihydroxy-21-[(3-sulphobenzoyl)oxy]pregna-1,4-diene-3-20-dione) and pharmacologically acceptable salts, especially the sodium salt, in the treatment of inflammatory bowel disease and especially Crohn's disease.

In particular, it provides a solid pharmaceutical composition having two or more pluralities of particles coated with a desired thickness of a polymethacrylate material to control the release profile of prednisolone metasulphobenzoate. It also provides use of coating thickness of the polymethacrylate material to control the release profile of prednisolone metasulphobenzoate through the intestinal tract.

Unless it is clear from the context that the free ester is intended, the term "prednisolone metasulphobenzoate" is used herein to include pharmacologically acceptable salts of prednisolone metasulphobenzoate as well as the free ester.

Inflammatory bowel disease covers chronic non-specific inflammatory conditions of the gastrointestinal tract, of which the two major forms are Crohn's disease and ulcerative colitis.

Crohn's disease may affect any part of the gastrointestinal tract although it frequently affects the small intestine, especially the ileum and may also affect the jejunum and any part of the colon, including the rectum, and especially the caecum. It is characterised by thickened areas of the gastrointestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa. The affected areas are often interspersed

with areas of relatively normal tissue.

Sulphasalazine has been used to treat cases of Crohn's disease affecting the colon as has 5-aminosalisylic acid in an enteric coated or slow release form. Steroids are widely used to treat severe cases of inflammation of the colon, especially ulcerative colitis and Crohn's disease. Usually they are administered orally or parenterally to provide a systemic effect, or rectally by enema to provide a topical effect. Relatively high doses of steroids are required to treat severe cases of inflammatory bowel disease. However, systemic absorption produces serious side effects and although systemic absorption is lower with rectal administration, enemas treat only the lower colon and rectum and their use is inconvenient.

The most commonly used steroid in the oral treatment of inflammatory bowel disease is prednisolone (17,21-di-hydroxypregna-1,4-diene-3,11,20-trione) in the form of the free alcohol or an ester thereof, usually the acetate. Daily doses of 15 to 60 mg (calculated as the free alcohol) are required to treat severe cases of inflammatory bowel disease, but absorption at these doses is harmful. Accordingly, present treatment with prednisolone is limited in both dosage and duration of therapy.

Several methods and compositions for targeting or controlling the release of an active compound to treat inflammatory bowel disease and Crohn's disease have been proposed.

US-A-4496553 relates to an oral pharmaceutical composition comprising 5-aminosalicylic acid (5-ASA) for the treatment of colitis ulcerosa or Crohn's disease. It discloses a slow-release tablet consisting of granules of 5-ASA coated with ethyl cellulose and compressed with microcrystalline cellulose granules, talc and sodium

stearate. Tests with ileostomy patients showed that 50% of the active ingredient from the tablets is released in the small bowel. It states (in column 6, lines 15-22) that release can be controlled by varying one or more of the particle size of the granulated active ingredient, the thickness and permeability of the coating, the active ingredient proper and the pH conditions within the coated particle.

EP-B-0097651 discloses a composition for selectively administering 5-aminosalicylic acid to the large intestine, comprising a solid oral dosage form containing the active compound, with a coating of a 60 to 150 micrometer thick layer of an anionic polymer which is insoluble in gastric juice and in intestinal fluid below pH 7 but soluble in colonic intestinal juice, so that the dosage form remains intact until the colon.

EP-B-0572486 discloses an orally administrable pharmaceutical dosage form which comprises a plurality of granules of a drug, such as 5-aminosalicylic acid, coated with a material which dissolves in the intestine and contained within a capsule which is also coated with a material which dissolves in the intestine. The composition is for selectively administering the drug to the intestine. It is stated that the granules are preferably contained within an enterically coated capsule which releases the granules in the small intestine and that the granules are coated with a coating which remains substantially intact until they reach at least the ileum and preferably thereafter provide a sustained release of the drug through the colon.

EP-A-0772443 discloses a non-disintegratable solid enteric pharmaceutical composition comprising prednisolone metasulphobenzoate having relatively rapid dissolution at pH 6.5 from an excipient matrix, and dosage forms containing

pellets of the composition. The rapid dissolution is increased by the presence of a rheological modifying super-disintegrant in an amount of at least 5% by weight, but insufficient to cause disintegration of the composition. It is stated that the composition may comprise a plurality of such pellets, which may be coated in an enteric coating such as cellulose acetate phthalate or, preferably, partly methyl esterified methacrylic acid polymers having a ratio of free acid groups to ester groups of about 1:2, contained in a capsule that is enterically coated with a suitable coating material. The coating material on the pellets is preferably one that is insoluble in gastric juices and intestinal fluid below pH 7, but is soluble in lower intestinal fluid. The enteric coating material of the capsule is chosen to protect the capsule during passage through the stomach. The composition is intended for use in the treatment of Crohn's disease.

EP-B-0502032 discloses a formulation for site specific release of an active compound in the colon for the treatment of diseases of the colon such as ulcerative colitis and Crohn's disease. The active may be, for example, prednisolone or 5-aminosalicylic acid among others. The formulation comprises an active compound and amorphous amylose with an outer coating of cellulose or an acrylic polymer material. The active compound is preferably coated with glassy amylose, which tends not to degrade until it reaches the colon where it is attacked by amylose cleaving enzymes provided by microbial flora normally present in the colon. The composition is further coated with a cellulose or acrylic polymer material, which enhances the delayed release property of the amylose-coated composition. The rate of release of the active compound from the composition once it reaches the colon may be controlled by varying the thickness of the inner amylose coating provided. It states that it is also possible to vary the release in the colon by coating different particles of the active compound with

amylose of different thicknesses. Release characteristics can be further varied by drying, which affects pore size and permeability or by adding a fatty or waxy substance to retard penetration of water. It is preferred that the cellulose or acrylic polymer outer coating material displays pH independent degradation.

WO-A-9921536 relates to a controlled release composition suitable for delivery of an active ingredient to the colon. It discloses a composition which comprises 5-aminosalicylic acid spheres also containing microcrystalline cellulose and having diameters in the range 1.00 to 1.40 mm, which spheres are coated with a mixed solvent (water and an organic water miscible solvent) amylose/ethyl cellulose composition, although the latter may instead be an acrylic polymer. The release profiles were examined for a range of amylose/ethyl cellulose ratios and coating thicknesses. It was found that coatings with a high proportion of ethyl cellulose resulted in very little drug release due to the absence of continuous amylose channels through the coat surface to the core of the pellet, whereas a coating with a high proportion of amylose resulted in films whose structure was compromised. Accordingly, where higher amylose concentrations were present in the coatings, a thicker coating was applied and the results showed that in such circumstances release of the active compound should not take place before the colon.

An improved method and composition for controlling release of an active agent such as prednisolone metasulphobenzoate to the intestinal tract would be desirable.

The inventors have now surprisingly found that employing the same pH dissolution dependent polymethacrylate material at different thicknesses on particles of prednisolone metasulphobenzoate results in release of

prednisolone metasulphobenzoate at different rates at the same pH and in a controllable manner over a range of pH values. The thickness of the polymethacrylate coating employed may be chosen, depending upon the pH and the desired rate and location of release, to provide a controlled release profile of prednisolone metasulphobenzoate. pH dissolution dependent coating materials such as polymethacrylates are usually employed to provide release of an active compound at a single location in the intestinal tract. To the best of our knowledge and belief, the use of different coating thickness of pH dissolution dependent coating materials have not been used to provide continual or sustained release.

Accordingly, in a first aspect of the invention there is provided an oral pharmaceutical composition comprising two or more pluralities of particles, said particles comprising prednisolone metasulphobenzoate, wherein the particles of each said plurality are coated with a different thickness of a polymethacrylate material to those of the or each other plurality, whereby prednisolone metasulphobenzoate is released at different locations in the intestinal tract.

Polymethacrylates which find particular utility in the present invention are anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios.

The polymethacrylates may be copolymers of acrylic acids (such as methacrylic acid) and acrylic acid esters (such as methyl methacrylate or ethyl ethacrylate). Preferably the polymethacrylates used in accordance with the present invention are methacrylic acid copolymers, which are based upon methacrylic acid and various acrylic acid esters (such as ethyl acrylate or methyl methacrylate) or mixtures thereof. More preferably, one or more copolymers of

methacrylic acid and methyl methacrylate, preferably having a ratio of free carboxyl groups to ester groups of, for example, about 1:2 (sold under the registered Trade Mark EUDRAGIT S by Röhm Pharma GmbH of Darmstadt, Germany) and having a molecular weight of 135,000 or about 1:1 (available from Röhm Pharma GmbH under the registered Trade Mark EUDRAGIT L) or a mixture thereof is used.

Preferably, the present invention utilises those polymethacrylates whose dissolution is pH-dependent. By polymethacrylates whose dissolution is pH-dependent, it is meant to include those polymethacrylates that, according to the current state of the art, are insoluble in gastric media until a certain pH is reached and those that give pH dependent release of a drug when used as a coating material, for example see The Handbook of Pharmaceutical Excipients, 3rd Edn., Edited by Arthur H. Kibbe (American Pharmaceutical Society and Pharmaceutical Press, 2000). Preferably, the polymethacrylate material comprises a polymethacrylate that is insoluble in gastric media until a certain pH is reached and/or gives pH dependent release of a drug when used as a coating material, according to The Handbook of Pharmaceutical Excipients whose monograph thereon on pages 401-406 is incorporated herein by reference.

Such polymethacrylates, whose dissolution is pH-dependent, include copolymers of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2 (available as EUDRAGIT S from Röhm Pharma GmbH) or about 1:1 (available as EUDRAGIT L from Röhm Pharma GmbH) and a copolymer of methacrylic acid and ethyl acrylate having a ratio of free carboxyl groups to ester groups of about 1:1 (available under the registered Trade Mark EUDRAGIT L 30 D-55 or EUDRAGIT L 100-55 from Röhm Pharma GmbH). More preferably, the polymethacrylate is one that is soluble at a pH greater than 5.5 and still more preferably at greater than 6.

Preferably, the polymethacrylate material coating the particles of each plurality of particles is the same as that coating those of the or each other plurality of particles.

In one embodiment of the invention, each of the pluralities of particles is coated with a different thickness of polymethacrylate material, whereby prednisolone metasulphobenzoate is released at locations around, but preferably before and after, the ileo-caecal valve.

Preferably there are two pluralities of particles, one plurality in which the particles are coated with a thickness of polymethacrylate material so as to release prednisolone metasulphobenzoate at the distal ileum before the ileo-caecal valve and the other plurality in which the particles are coated with a different thickness of polymethacrylate material so as to release prednisolone metasulphobenzoate at the proximal caecum, after the ileo-caecal valve. Preferably the polymethacrylate material is a methacrylic acid copolymer, more preferably a copolymer of methacrylic acid and methyl methacrylate, preferably having a ratio of free carboxyl groups to ester groups of about 1:2.

Preferably, the polymethacrylate coating on the particles are of a thickness corresponding to a theoretical weight gain on coating of 15% for one of the pluralities and 20% weight gain for the other and preferably the number of particles in each plurality are present as a ratio of 15% weight gain coated particles to 20% weight gain coated particles of 1:3.

In another embodiment of the invention, the particles of each of the pluralities may be coated with a different thickness of polymethacrylate material chosen at increments to provide a homogeneous release profile of prednisolone metasulphobenzoate along at least one selected portion of

the intestinal tract or along the entire intestinal tract.

Preferably, the thickness of the polymethacrylate material and the incremental differences are chosen to provide multi-site release of prednisolone metasulphobenzoate such that release of the drug is homogeneous through the intestine and preferably along the ileum and the colon, particularly the ascending colon.

In this embodiment, the invention may provide homogeneous release of prednisolone metasulphobenzoate that has the advantage over conventional sustained release preparations in that the incremental differences in thickness of polymethacrylate material can be chosen to overcome the variations in pH and the varied rate of progression or transit of a capsule or tablet through the intestine.

In conventional sustained release preparations, the variation in the rate of progression through the intestinal tract may result in delivery of prednisolone metasulphobenzoate to certain parts of the intestine at a lower concentration than to other parts. Similarly, the variation in pH in different parts of the intestine tends to result in different rates of release from conventional sustained release preparations. This may result in a loss of effect.

In patients with inflammatory bowel disease, especially with active inflammation, the rate of transit through the intestine and the pH within the intestine are often abnormal. Conventional sustained release formulations which provide release of the active agent in a time or pH-dependent manner may not provide a predictable or effective delivery of the active agent to the target areas of the intestine. Such formulations can result in underdosing at certain sites or overdosing, "dose-dumping", at other sites.

In the present embodiment, such variations can be accounted for by, for example, coating particles of each plurality of particles with a chosen thickness of polymethacrylate material to provide multi-site release throughout the intestine, wherein the incremental differences in coating thickness between each plurality may vary. For example, in order to obtain homogeneous release to parts of the intestine through which there is a greater rate of passage and to parts with a lesser rate of passage, the incremental differences in coating thickness for the pluralities of particles being delivered to the part of the intestine with a greater rate of passage will be smaller than to that with a lesser rate of passage, and/or the number of particles in the plurality of particles delivered to the part with greater rate of passage will be larger. Similarly, in order to provide homogeneous release to parts of the intestine with higher pH and with lower pH, a thicker coating should be provided on the particles that are intended to release prednisolone metasulphobenzoate to the part of the intestine with the higher pH, although this will depend upon its location within the intestine. In this way, the rate of release of prednisolone metasulphobenzoate may be controlled in relation to variations in pH or transit through the intestine, without being solely dependent upon either a specific pH being reached or a specific time having elapsed before release of prednisolone metasulphobenzoate.

In order to further control the release profile of the drug through the intestine, particles from one plurality of particles may be coated with a different coating material to those of another plurality of particles. Particles of one plurality may also be of a different size to those of another plurality.

In a preferred embodiment of the present invention, the composition further comprises a capsule, preferably an

enterically coated capsule, within which the pluralities of particles are contained. The capsule will usually be a soft, or preferably, hard gelatine capsule, although other capsules which will dissolve in the small intestine may be used. The enteric coating will protect the capsule during its passage through the stomach. Any suitable enteric coating material which is soluble in the small intestine can be used. For example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate or initially ethyl cellulose followed by polyvinyl acetate phthalate may be used, but it is preferred to use an anionic polymer having an appropriate dissolution profile. The presently preferred polymers are anionic carboxylic, that is polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the polymers should be acrylic polymers and the presently preferred polymers are copolymers of methacrylic acid and methyl methacrylate in which the ratio of free acid groups to ester groups is about 1:1 (i.e. Eudragit L).

Alternatively, the particles may be compressed into a tablet, which may be enterically coated.

The capsule (or other dosage form) coating can and usually will contain plasticiser and possibly other coating additives such as colouring agents, gloss producers, talc and/or magnesium stearate as well known in the coating art. In particular, anionic carboxylic acrylic polymer coatings usually contain 10 to 25% by weight of a plasticiser, especially diethyl phthalate.

In a second aspect of the invention there is provided the use of the coating thickness of a pH dissolution dependent polymethacrylate material on particles comprising prednisolone metasulphobenzoate to control the release profile of prednisolone metasulphobenzoate in the intestinal

tract. By pH dissolution dependent polymethacrylate material, it is meant polymethacrylate materials whose dissolution is dependent upon pH, as defined above with reference to The Handbook of Pharmaceutical Excipients. For example, a polymethacrylate material which is insoluble at pH 2, but substantially soluble at greater than pH 5.5 is a pH dissolution dependent polymethacrylate material.

In a third aspect of the present invention, there is provided use of a polymethacrylate material in the preparation of a medicament as described above for the treatment of disorders of the intestinal tract. Preferably, the medicament will be for use in the treatment of Crohn's disease.

In a fourth aspect of the present invention, there is provided a method of treating Crohn's disease, said method comprising administering to a patient an effective amount of prednisolone metasulphobenzoate in two pluralities of particles each coated with a different thickness of polymethacrylate material to release prednisolone metasulphobenzoate at locations before and after the ileo-caecal valve of the patient.

The particles used in the present invention are typically pellets or granules.

The particles according to the present invention may be pellets having a diameter in the range 500 to 2500 μm, preferably 800 to 1700 μm, more preferably 800 to 1500 μm and still more preferably 1000-1500 μm. However, it should be appreciated that particles may have a diameter anywhere within the aforementioned ranges, or outwith, and that a single dosage form according to the present invention may have particles of one or more diameter or range of diameters.

It should be appreciated that the actual coating thickness for any particular weight gain of coating depends upon the size and weight of the particles.

Preferably the coating thickness according to the present invention is in the range 5% to 30%, more preferably 10% to 25% and most preferably about 15% and about 20%.

The invention will now be illustrated by the following non-limiting Examples with reference to the accompanying Figures.

Figure 1 is a graph of percentage release (% Release), of prednisolone metasulphobenzoate from pellets coated with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to a theoretical weight gain of 5%, 15% and 25%, against time;

Figure 2 is a graph of percentage release (% Release), of prednisolone metasulphobenzoate from pellets coated with with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to a theoretical weight gain of 15%, against time at a pH of 6.0, 6.2, 6.6 and 7.2;

Figure 3 is a graph of percentage release (% Release), of prednisolone metasulphobenzoate from pellets coated with with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to a theoretical weight gain of 15% and a particle size of up to 1500 μm and of up to 2000 μm, and pellets coated with a mixed polymethacrylate coating of 5% of a methacrylic acid ethyl acrylate copolymer with a ratio of free carboxyl groups to ester groups of 1:1 and 95% of a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of

1:2 to 15% weight gain, against time.

Example 1

Prednisolone metasulphobenzoate pellets were prepared by preparing a dry mix of 5 wt% prednisolone sodium metasulphobenzoate, 40 wt% microcrystalline cellulose (Avicel™ PH 101), 35 wt% lactose monohydrate (D80 200 Mesh) and 30 wt% croscarmellose sodium (Ac-Di-Sol™). Purified water (185 wt%) was added and the resulting mixture mixed for 10 minutes to form and extrudable paste which was then extruded from a 25 mm diameter bowel through a 1 mm diameter tube of about 5 mm length at a rate of about 100 mm/min, using a Niro Fielder Type E140 extruder, and spheronised in a Nica System Spheroniser S700 on a 20 cm plate rotated at about 33 rpm. The pellets were then dried in a fluid bed granulator and screened to ensure the size of the particles was in the range 800 to 1500 μm.

The pellets were then spray coated with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to provide three batches having a theoretical weight gain on coating (weight gain) of 5%, 15% and 25%.

The rate of release of prednisolone metasulphobenzoate from pellets having different thicknesses of coating and at a range of pH values was investigated.

Example 2

The effect on the rate of release of prednisolone metasulphobenzoate from pellets having a coating of 5%, 15% and 25% weight gain, prepared as described in Example 1, was studied in a dissolution apparatus by stirring the pellets in a tribasic sodium phosphate medium at pH 6 and

withdrawing samples at 15 minute intervals to measure, by HPLC, the amount of prednisolone metasulphobenzoate in solution. The results are shown in Figure 1.

As can be seen from Figure 1, increasing the thickness of the coating significantly decreases the rate of drug release. The 5% weight gain coated pellets provide complete (100%) drug release within 15 minutes. The 15% weight gain coated pellets, however, provided 50% drug release after about 45 minutes and 100% drug release after about 100 minutes and the 25% weight gain coated pellets provided 50% drug release after 120 minutes and 100% drug release after about 300 minutes.

It is particularly surprising that particles coated with the same pH dissolution dependent coating material, but at different thicknesses provide drug release at such significantly different rates at the same pH.

Example 3

The effect of pH on the rate of drug release from a coated pellet having a 15% weight gain coating prepared according to Example 1 was investigated. The pellets were subjected to drug release studies as described in Example 2 only using a pH of 6.0, 6.2, 6.6 and 7.2. Figure 2 illustrates the pH dependent nature of drug release from coated pellets having a 15% weight gain coating.

As can be seen from Figure 2, at pH 6, complete drug release occurs at about 120 minutes, with 50% drug release at about 45 minutes. At higher pH, the rate of drug release increases until at pH 7.2, complete drug release occurs after about 30 minutes.

Example 4

In order to investigate the effect of the precise coating composition on drug release, two batches of prednisolone metasulphobenzoate pellets having a 15% weight gain of either of two selected polymethacrylate coating materials were prepared by the method of Example 1. Pellets of the first batch were coated with a mixed polymethacrylate coating of 5% of a methacrylic acid ethyl acrylate copolymer with a ratio of free carboxyl groups to ester groups of 1:1 and 95% of a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to 15% weight gain. Pellets of the second batch were coated with a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of 1:2 to a weight gain of 15%.

The effect of coating composition on drug release was investigated by subjecting the two batches of pellets to a drug release study of the type described in Example 2. The results are illustrated in Figure 3.

As can be seen from Figure 3, batch 1, of which pellets are coated with a mixture of polymethacrylates - one which dissolves at pH 6.0 and one which dissolves at pH 5.5 - released drug at a greater rate than batch 2, of which pellets were coated with a polymethacrylate which dissolves at pH 6.0 to 7.0.

Example 5

In order to investigate the effect of pellet size on drug release, prednisolone metasulphobenzoate pellets were prepared in two batches using the method of Example 1; the first batch having a diameter of up to 2000 μm and the second of up to 1500 μm and both having a coating of a copolymer of methacrylic acid and methyl methacrylate having

a ratio of free carboxyl groups to ester groups of 1:2 to a weight gain of 15%. The pellets were subjected to a drug release study as per Example 4. The results of this are also shown in Figure 3.

As Figure 3 shows, increasing the pellet size resulted in a decrease in the rate of drug release. It is likely that this is because a larger pellet having a particular percentage weight gain of coating has a thicker coat than a smaller pellet with the same percentage weight gain of coating, because the ratio of surface area to weight is lower for the larger pellet.

CLAIMS

1. An oral pharmaceutical composition comprising two or more pluralities of particles, said particles comprising prednisolone metasulphobenzoate, wherein the particles of each said plurality are coated with a different thickness of a polymethacrylate material to those of the or each other plurality, whereby prednisolone metasulphobenzoate is released at different locations in the intestinal tract.

2. A composition as claimed in Claim 1, wherein the polymethacrylate material is a pH dissolution dependent polymethacrylate material.

3. A composition as claimed in Claim 1 or Claim 2, wherein the particles of each plurality are coated with the same polymethacrylate material as those of the or each other plurality.

4. A composition as claimed in any one of the preceding claims, wherein the polymethacrylate material comprises a methacrylic acid copolymer.

5. A composition as claimed in claim 4, wherein the polymethacrylate comprises a copolymer of methacrylic acid and methyl methacrylate.

6. A composition as claimed in Claim 5, wherein the polymethacrylate is selected from a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2, a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:1 or a mixture thereof.

7. A composition as claimed in any one of the preceding claims, wherein the particle has a diameter in the range 800

to 1500μm.

8. A composition as claimed in Claim 7, wherein the particles are coated with the polymethacrylate material to a theoretical weight gain on coating in the range 5% to 30%.

9. A composition as claimed in Claim 8, wherein the particles are coated with the polymethacrylate material to a theoretical weight gain on coating in the range 10% to 25%.

10. A composition as claimed in any one of the preceding claims, wherein each of said pluralities of particles is coated with a different thickness of the polymethacrylate material, whereby prednisolone metasulphobenzoate is released at locations before and after the ileo-caecal valve.

11. A composition as claimed in Claim 10, wherein there are two pluralities of particles.

12 A composition as claimed in Claim 10 or Claim 11, wherein the particles are coated with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2.

13. A composition as claimed in Claim 12, wherein a first plurality of particles is coated to provide a theoretical weight gain of 15% and a second plurality of particles is coated to provide a theoretical weight gain of 20%.

14. A composition as claimed in Claim 13, wherein the first and second pluralities of particles are present in a ratio of about 1:3.

15. A composition as claimed in any one of Claims 1 to 9, wherein the thickness of polymethacrylate material coating

particles of each plurality of particles is of increments chosen to provide a homogeneous release profile of prednisolone metasulphobenzoate along at least one selected portion of the intestinal tract.

16. A composition as claimed in any one of the preceding claims, which further comprises an enterically coated capsule within which the pluralities of particles are contained.

17. Use of the coating thickness of a pH dissolution dependent polymethacrylate material on particles comprising prednisolone metasulphobenzoate to control the release profile of prednisolone metasulphobenzoate in the intestinal tract.

18. A use as claimed in Claim 17, wherein the polymethacrylate material comprises a methacrylic acid copolymer.

19. A use as claimed in Claim 18, wherein the polymethacrylate comprises a copolymer of methacrylic acid and methyl methacrylate.

20. A use as claimed in Claim 19, wherein the polymethacrylate is selected from a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2, a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:1 or a mixture thereof.

21. An oral composition as defined in any one of Claims 1 to 16 for use in therapy or diagnosis practised on the human or animal body.

22. Use of a polymethacrylate material in the preparation

of a medicament as defined in any one of Claims 1 to 16 for the treatment of disorders of the intestinal tract.

23. Use of a polymethacrylate material in the preparation of a medicament as defined in any one of Claims 1 to 16 for the treatment of Crohn's disease.

24. A use as claimed in Claim 22 or Claim 23, wherein the polymethacrylate material is a pH dissolution dependent polymethacrylate material.

25. A method of treating Crohn's disease, said method comprising administering to a patient an effective amount of prednisolone metasulphobenzoate in two pluralities of particles each coated with a different thickness of polymethacrylate material to release prednisolone metasulphobenzoate at locations before and after the ileo-caecal valve of the patient.

26. A composition as claimed in Claim 1 substantially as hereinbefore described with reference to the Examples.

27. A use as claimed in Claim 17 substantially as hereinbefore described with reference to the Examples.

28. A use as claimed in Claim 22 substantially as hereinbefore described with reference to the Examples.

ABSTRACT

Controlled Release Composition for the Treatment of Inflammatory Bowel Disease

Irritable bowel disease and especially Crohn's disease are treated by administration of a controlled release prednisolone metasulphobenzoate composition comprising at least two pluralities of particles of prednisolone metasulphobenzoate in an enterically coated capsule, in which the particles of each plurality are coated with a different thickness of a polymethacrylate material, which is preferably pH dissolution dependent, to those of the or each other plurality, providing release of prednisolone metasulphobenzoate at chosen locations in the intestinal tract and especially providing homogeneous release throughout a chosen portion of the intestinal tract.

FIGURE 1

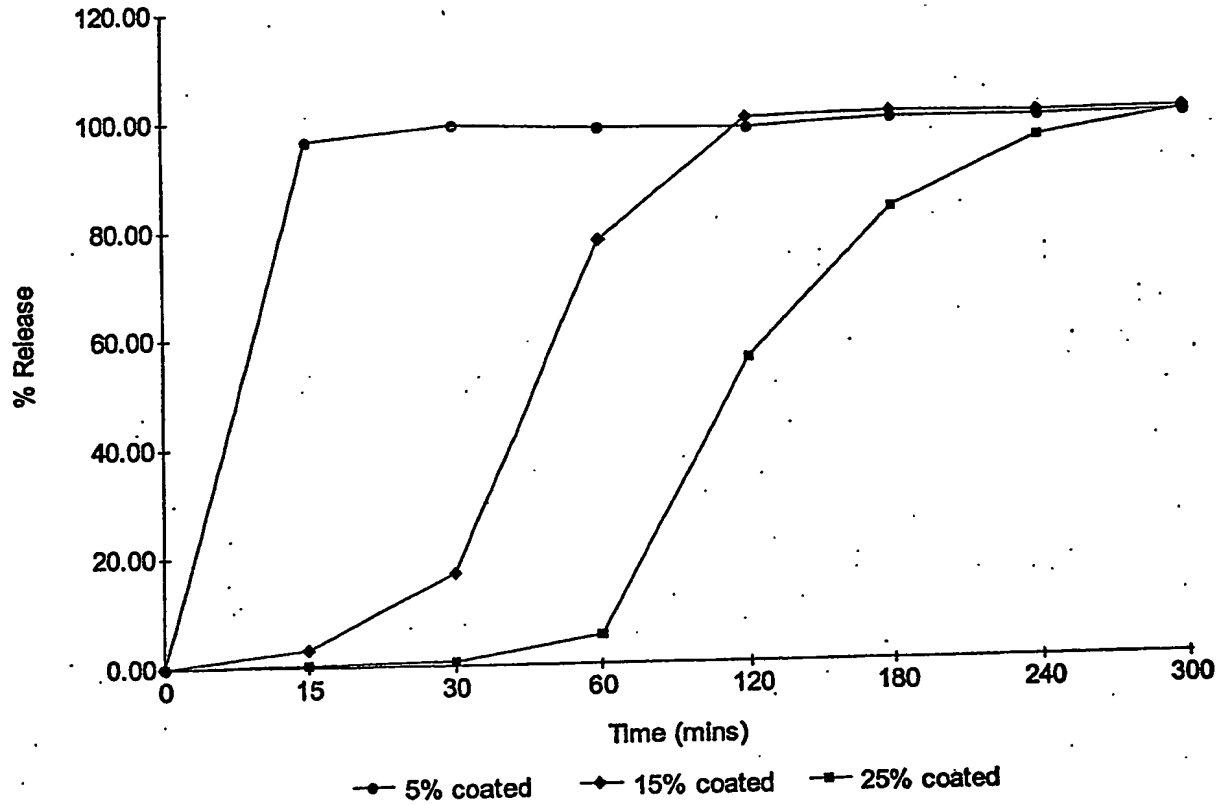

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Release
0
15
30
60
120
180
240
300
Time (mins)
5% coated
15% coated
25% coated

FIGURE 2

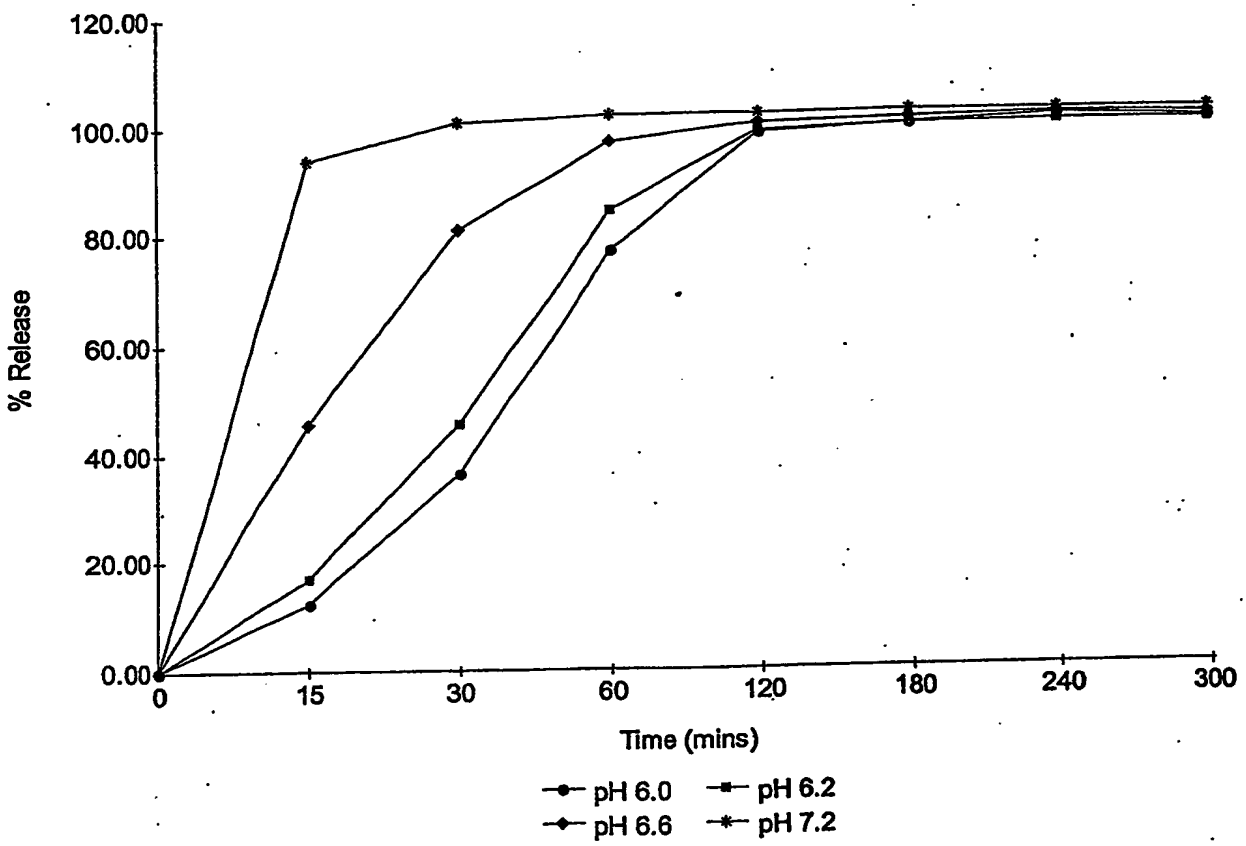
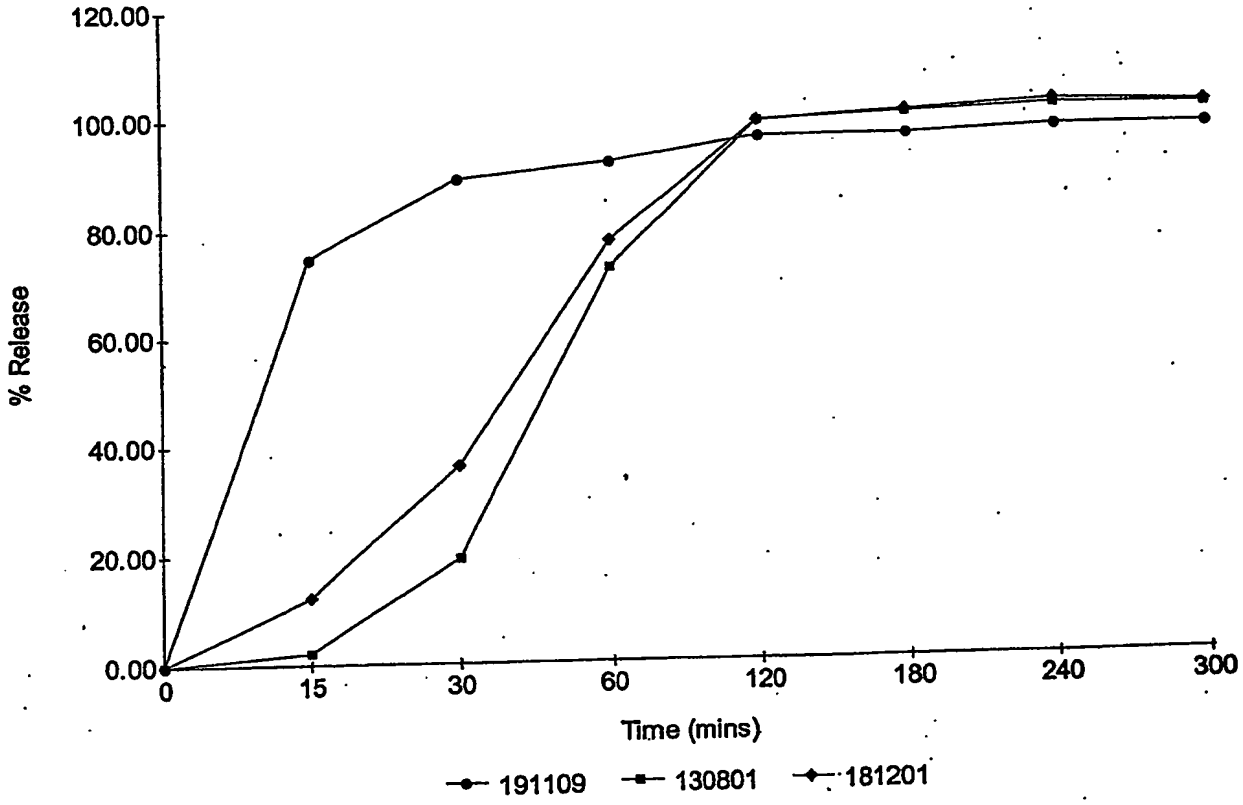

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Release
0
15
30
60
120
180
240
300
Time (mins)
pH 6.0
pH 6.2
pH 6.6
pH 7.2

FIGURE 3


120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Release
0
15
30
60
120
180
240
300
Time (mins)
191109
130801
181201